Expert opinion of the Heart Failure Working Group of the Polish Cardiac Society on the use of dapagliflozin in the treatment of heart failure with reduced ejection fraction

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ABSTRACT

Heart failure (HF) is a global health problem inherent in an aging population with coexisting cardiovascular diseases. Based on data from the Polish National Health Fund (Polish, Narodowy Fundusz Zdrowia), approximately 1.2 million people in Poland currently suffer from HF, and 140 000 of them die annually. Recently, Poland was ranked fifth among the European Union countries regarding the number of patients with diagnosed HF and first in terms of the number of HF hospitalizations (547 per 100 000 population) among 34 countries associated in the Organization for Economic Cooperation and Development. In recent years, a significant progress has been made in the diagnosis and treatment of HF with reduced left ventricular ejection fraction (HFrEF), which has resulted in a reduction in cardiovascular and total mortality. Despite these advantages, 5-year survival in the course of HF is still worse than that observed in some types of cancer, both in the populations of men and women. Hence, the search for drugs improving the prognosis in this group of patients is still ongoing. Sodium-glucose cotransporter 2 inhibitors represent a new group of drugs that will undoubtedly be a milestone in the treatment of patients with HFrEF. This expert opinion covers the history of dapagliflozin, which, from a drug dedicated to the treatment of type 2 diabetes, has become one of the most effective drugs improving prognosis and quality of life as well as reducing the number of hospitalizations in patients with HF. This document presents the opinion from the experts of the Heart Failure Working Group of the Polish Cardiac Society on the most relevant studies on dapagliflozin and indications for its use.

Epidemiology of heart failure Heart failure (HF) is a health problem characteristic of an aging population burdened with cardiovascular diseases.[1] According to epidemiological data, HF affects about 64 million people worldwide,[2] and this number will undoubtedly increase due to increasing life expectancy.[3] The risk of developing HF increases with age and was assessed as follows: 28.5% for women and 33% for men over 55 years of age.[4] Heart failure is associated with poor prognosis, as evidenced by high rates of hospitalization and mortality (about 40% of patients die within 5 years after their first hospitalization for HF).[5,6] In Poland, as many as 53% of patients with HF are readmitted to the hospital, and every fourth patient requires rehospitalization within 30 days of discharge.[5,6] Although cardiovascular mortality has decreased in recent years, deaths due to HF have not.[7,8] Forecasts for the coming years indicate that the number of people affected by HF will increase by nearly 25%, which will cause a significant societal burden.[9] Therefore, HF is now seen as an epidemic of the 21st century.

According to our studies based on data from the Polish National Health Fund (Polish, Narodowy Fundusz Zdrowia [NFZ]), about 1.2 million people have HF in Poland, of whom 140 000 die every year. In 2017, Poland was ranked fifth among the European Union countries in terms of the number of patients with HF (1130 cases per 100 000 population) and first among 34 countries of the Organization for Economic Co-operation and Development (OECD) in terms of the number of hospitalizations due to HF (547 cases per 100 000 population).[10,11] The current situation regarding HF in Poland was most comprehensively presented by the Ministry of Health in the report on HF (prepared as part of the Health Needs Maps—Database of Systemic and Implementation Analysis project), based on data from NFZ (2009–2018) and Ministry of Digital Affairs (2013–2018).[12]

Based on that analysis, we know that 2 327 399 people were treated for HF in Poland in the years 2009 to 2018. That population was dominated by women (constituting 56.3%). A gradual 11.9% increase in prevalence was observed from 1 122 877 cases (2890 per 100 000 population) in 2013 to 1 242 129 cases (3233 per 100 000 population) in 2018. This increase was most visible in women and patients with the disease of ischemic etiology.

Unmet needs in the treatment of patients with heart failure In recent years, a significant progress has been made in the diagnosis and treatment of patients with HF with reduced left ventricular ejection fraction (HFrEF), which has resulted in a reduction in cardiovascular and total mortality. β-Blockers, mineralocorticoid receptor antagonists (MRAs), and inhibitors of the renin–angiotensin–aldosterone system, including angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), have been used as triple therapy for HFrEF over the past years, partially changing the course of the disease. Despite that, 5-year survival in patients with HF is still worse than that observed in some types of cancer (except for lung cancer), in both men and women.[13] Therefore, there is still a need for new, effective therapies for HF. Patients with HF constitute a very difficult-to-treat population owing to the frequent presence of comorbidities. According to the European Society of Cardiology Heart Failure Pilot Study database, as many as 74% of patients with HF have at least one comorbid disease, and 20% to 25% have 5 comorbidities.[14] According to the available data, coronary artery disease is one of the major reasons of HFrEF. The most common comorbidities include arterial hypertension, chronic obstructive pulmonary disease, renal failure, and anemia.[15] Moreover, type 2 diabetes (T2D) is also often associated with HF. Its prevalence in patients with HF ranges from 12% to 30% in the general population and from 15% to 47% in clinical trials.[16] In patients with T2D, HF develops about 2.5-fold more frequently than in those without T2D, and T2D develops more often in patients with HF than in those without HF. In patients with T2D, the development of HF represents one of the most common early cardiovascular complications.[16,17]

Among patients with HF in Poland, frequent hospitalizations pose the biggest problem; the most common reason for hospitalization, particularly in people over 65 years of age, is cardiovascular decompensation, indicating disease progression.[6] Exacerbations of HF are significantly life-threatening and lead to a gradual deterioration of health and, most importantly, shortening of life.[18] In Poland, more than half of patients with HF are readmitted to the hospital, and every fourth patient returns to the hospital within 30 days after discharge.[6] As many as 11% of patients die within 1 year of hospitalization due to cardiovascular decompensation.[6,18] The results of groundbreaking research on HF have recently been published and showed a reduction in mortality and the frequency of hospitalization. They concern 2 new groups of drugs—angiotensin receptor–neprilysin inhibitors (ARNIs), represented by sacubitril/valsartan; and sodium-glucose cotransporter 2 (SGLT-2) inhibitors (flozins), represented by dapagliflozin, empagliflozin, and canagliflozin. Previous large randomized clinical trials on the use of SGLT-2 inhibitors in patients with T2D have reported a reduction in cardiovascular risk, including a decrease in the number of hospitalizations for HF[19-21]; however, HF was not an inclusion criterion in those studies.

In the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) study, the results of which were announced at the European Congress of Cardiology in Paris on September 1, 2019 and simultaneously published in the *New England Journal of Medicine*, for the first time, the attention was focused on patients with HF, regardless of whether they were diagnosed with T2D or not. In that study, SGLT-2 inhibitor treatment (dapagliflozin) prevented relapses and exacerbations of HF and reduced cardiovascular mortality.[22] It is also interesting that the observed benefits of dapagliflozin were independent of the presence of T2D. In the context of those pioneering results, we are witnessing a breakthrough in the treatment of HF. In the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Reduced Ejection Fraction) study, which compared the effects of empagliflozin in patients with HFrEF regardless of the presence of T2D, empagliflozin was shown to decrease the number of cardiovascular deaths or HF hospitalizations (primary endpoint) by 25% and reduce the number of the first and subsequent hospitalizations for HF (secondary endpoint) by 30%.[23]

Premises for the use of SGLT-2 inhibitors in heart failure SGLT-2 inhibitors constitute a new group of drugs that were initially dedicated to treat patients with T2D. However, recent large, randomized clinical trials—particularly those with dapagliflozin or empagliflozin—have revealed their great value in reducing cardiovascular complications, particularly associated with HF not only in patients with coexisting T2D (DECLARE-TIMI 58 [Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events] and EMPA-REG OUTCOME [Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients] studies) but also in those with HFrEF regardless of T2D diagnosis (the DAPA-HF and EMPEROR-Reduced studies).

The complex and multidirectional mechanism of action of these drugs has a beneficial effect on both the control of T2D and the reduction of cardiovascular complications. SGLT-2, which is present in the proximal renal tubules, is responsible for most of the reabsorption of filtered glucose from the lumen of the tubule. By inhibiting SGLT-2, dapagliflozin reduces glucose reabsorption and lowers the renal glucose threshold, thus increasing urinary glucose excretion.[24] This effect is independent of insulin (both in terms of its secretion and its action) and—very importantly—is achieved without the risk of hypoglycemia. Reducing glucose reabsorption, and thus increasing its excretion with urine, favors a negative energy balance. This results in weight loss and improves insulin sensitivity, and the reduction in glucotoxicity could have a protective effect on pancreatic β cells.[25]

The benefits of using SGLT-2 inhibitors are not limited to their effects on glucose reabsorption. Dapagliflozin also reduces sodium reabsorption and increases its delivery to the macula densa, which regulates afferent arteriole tone through the tubuloglomerular feedback. The nephroprotective effect resulting from the contraction of the renal afferent arterioles reduces intraglomerular hyperfiltration and excretion of urinary albumin. The cardiovascular effect includes improved hemodynamics and results from increased osmotic diuresis, decreased plasma volume, and decreased blood pressure, which leads to lower left ventricular preload and afterload.[26] Another relevant factor is the beneficial effect on the energy of the cardiac muscle. SGLT-2 inhibitors increase the production of ketone bodies and their use in the heart, which improves the energy metabolism of the cardiac muscle and reduces the risk of HF development and recurrence.[27] Unfavorable remodeling of the heart is also inhibited.[28]

Recently, studies of patients with HFrEF without T2D (DAPA-HF and EMPEROR-Reduced) have been completed. However, studies are still ongoing in patients with HF with preserved ejection fraction without T2D (EMPEROR-Preserved and DELIVER [Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure]).

As outlined above, the DAPA-HF study was the first major clinical trial to analyze patients with HF without T2D. In that study, dapagliflozin significantly reduced the risk of cardiovascular death and hospitalization due to HF. This effect was equally evident both in patients with T2D and those without concomitant disorders of carbohydrate metabolism. Patients taking dapagliflozin had less severe HF symptoms than those taking placebo, which translated into a better quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ).

European Society of Cardiology / European Association for the Study of Diabetes guidelines on the use of SGLT-2 inhibitors in the treatment of type 2 diabetes In 2019, the new European Society of Cardiology guidelines for the management of diabetes, prediabetes, and cardiovascular diseases were developed in cooperation with the European Association for the Study of Diabetes.[29] The presented information indicated the extremely important role of SGLT-2 inhibitors in patients with T2D and cardiovascular diseases, clearly emphasizing the paradigm shift in the treatment of this group of patients. The role of SGLT-2 inhibitors in patients with T2D and cardiovascular disease was analyzed based on 4 large cardiovascular outcome trials (CVOTs): EMPA-REG OUTCOME,[19]

CANVAS (Canagliflozin Cardiovascular Assessment Study),[20] DECLARE-TIMI 58,[21] and CREDENCE (Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy).[30] Those were the first studies to assess the effect of this class of drugs in T2D, not only in terms of metabolic benefits but also reduction of cardiovascular complications. Those studies were performed in diverse populations. Almost all patients in the EMPA-REG OUTCOME study[19] had cardiovascular disease, whereas only 40% of individuals in the DECLARE-TIMI 58 study had diagnosed cardiovascular disease,[21] with the remaining 60% of patients having at least one of the 3 risk factors (smoking, hypertension, and hyperlipidemia). For the first time in the history of T2D studies, we have data from several CVOTs indicating a reduction in cardiovascular complications following the use of hypoglycemic drugs in patients with diagnosed cardiovascular diseases and those at high or very high cardiovascular risk. Based on the results of the abovementioned large randomized trials, the authors of the guidelines recommend (class IA) the use of SGLT-2 inhibitors (dapagliflozin, empagliflozin, and canagliflozin) to reduce the risk of HF in patients with T2D who either have cardiovascular disease or are at high or very high cardiovascular risk. In people with high or very high cardiovascular risk or multiple cardiovascular risk factors, the recommendation is to start T2D treatment with SGLT-2 or glucagon-like peptide 1 inhibitors as monotherapy and to add metformin as second-line treatment if this is ineffective. When a patient with T2D and cardiovascular risk factors is treated with metformin, adding an SGLT-2 inhibitor is recommended to reduce the risk of cardiovascular events.[29]

Of note, at the time the abovementioned guidelines were developed, the results of the DAPA-HF study were not available yet. That study examined the effect of dapagliflozin in patients diagnosed with HFrEF, regardless of the presence of carbohydrate metabolism disorders.

The DECLARE-TIMI 58 study and its subanalysess

The DECLARE-TIMI 58 study[21] evaluated patients at 40 years of age and older who were diagnosed with T2D and had glycated hemoglobin (HbA_{1c}) levels in the range of 6.5% to 12%, an estimated glomerular filtration rate (eGFR) greater than or equal to 60 ml/min/1.73 m^2, and diagnosed cardiovascular disease or cardiovascular risk factors. Patients were randomized to receive dapagliflozin 10 mg daily or placebo. The authors of the study emphasized a good control of other cardiovascular risk factors—ie, appropriate mean values of both blood pressure and low-density lipoprotein cholesterol. During over 4 years of follow-up, treatment with dapagliflozin significantly reduced the composite endpoint (incidence of cardiovascular deaths and the number of HF hospitalizations), although it did not lower the incidence of major adverse cardiovascular events defined as cardiovascular mortality, myocardial infarction, and stroke.

The analysis of the DECLARE-TIMI 58 study by Kato et al[31] provided further evidence of clinical benefits, particularly in patients with T2D and coexisting HF. Kato et al[31] assessed the effect of dapagliflozin added to standard pharmacological treatment in patients with HFrEF (defined as left ventricular ejection fraction below 45%). The effect of dapagliflozin treatment on the frequency of renal events (ie, deterioration of eGFR by more than 40% and the occurrence of end-stage renal disease or death due to renal causes) was also assessed.[31] There was a significant reduction in the primary composite endpoint (cardiovascular death or hospitalization for HF) in patients with HFrEF treated with dapagliflozin versus placebo. Although the effect of dapagliflozin on the incidence of hospitalizations for HF was consistent in patients with or without HFrEF, a significantly greater decrease in cardiovascular deaths was observed in patients with HFrEF. A reduced risk of all-cause mortality was also observed with dapagliflozin treatment in patients with HFrEF compared with those without HFrEF. In patients with HFrEF, the benefits of dapagliflozin in reducing cardiovascular deaths or hospitalizations for HF appeared early and were sustained throughout the study.

Another benefit of dapagliflozin in the DECLARE-TIMI 58 study was the improvement of kidney function. Dapagliflozin treatment resulted in a reduction in the incidence of combined events including a sustained decline in eGFR, development of end-stage renal disease, renal death, or cardiovascular death. The difference between groups in favor of dapagliflozin was observed owing to a reduction in renal events (ie, sustained decline in eGFR, end-stage renal disease, and renal death). In addition, dapagliflozin decreased the incidence of new cases of persistent albuminuria and led to a reduction in macroalbuminuria compared with placebo.

The DAPA-HF study and subgroup analysis

The results of the DECLARE-TIMI 58 study were one of the reasons for the search for further evidence of the beneficial effect of dapagliflozin on reducing cardiovascular mortality in patients with HF without diagnosed T2D. The randomized, double-blind, placebo-controlled DAPA-HF study assessed the efficacy and safety of dapagliflozin versus placebo (added to standard treatment) in patients with HFrEF.[22] The study included patients older than 18 years of age diagnosed with HFrEF (lasting for at least

2 months) with New York Heart Association (NYHA) functional class II to IV symptoms during the optimal target pharmacological and interventional treatment (eg, if they were eligible for implantation of a cardioverter-defibrillator or cardiac resynchronization therapy).[22,32] Pharmacotherapy, in line with the current guidelines for the management of HF, was based on ACEIs / ARBs or sacubitril / valsartan and a β-blocker and / or MRA, consisting of individualized, stable (for at least 4 weeks) drug doses (except for symptom-dependent diuretics). The DAPA-HF inclusion criteria also included elevated levels of N-terminal fragment of the prohormone brain natriuretic peptide (≥600 pg/ml or ≥400 pg/ml if the patient had an episode of decompensation due to HF in the year before enrollment, or ≥900 pg/ml if the patient had coexisting atrial fibrillation or atrial flutter). For patients with T2D (about 42% of enrolled patients and an additional 3% diagnosed during the study), antidiabetic drugs were modified as needed (eg, reducing insulin and sulfonylurea doses to avoid hypoglycemic episodes), particularly in patients with HbA_{1c} below 7%. For the first time in studies with dapagliflozin, patients with chronic kidney disease (ie, with an eGFR of 30 to 60 ml/min/1.73 m^2) were included. Patients were then randomized (1:1) to receive dapagliflozin orally at a dose of 10 mg once daily or placebo.

The primary endpoint of the study was the time to the composite endpoint, which included cardiovascular death, hospitalization for HF, or an urgent visit for HF. The secondary endpoints were as follows: cardiovascular mortality or hospitalization for HF, the total number of hospitalizations (first and subsequent) for HF and cardiovascular deaths, improvement in the quality of life based on the change from baseline in the KCCQ questionnaire after 8 months of follow-up,[33] worsening of renal function (ie, persistent decline in eGFR by ≥50% or end-stage renal disease defined as persistent eGFR decline <15 ml/min/1.73 m^2, chronic renal dialysis, or kidney transplant) or renal death, and death from any cause. The final analysis included 4744 patients who were followed up for a median of 18 months.

The DAPA-HF study showed: a 26% relative reduction in the primary composite endpoint (P <0.0001), a 18% reduction in the relative risk of cardiovascular death, a 30% reduction in the relative risk of worsening / hospitalization for HF, a 17% reduction in the relative risk of death from any cause, improvement in the quality of life and lower intensity of HF symptoms based on the results of the KCCQ questionnaire at 8 months compared with baseline. In addition, the safety of dapagliflozin was similar to placebo in terms of its effects on volume depletion, renal dysfunction, and hypoglycemia, regardless of the presence of T2D.

The results obtained in patients with T2D were similar to those of patients without. The positive effects of dapagliflozin on the reduction of cardiovascular deaths and the risk of HF worsening, as compared with placebo, were visible by day 28 of therapy and did not depend on the HF treatment used.[34,35] The benefits of dapagliflozin were also similar regardless of left ventricular ejection fraction. The subgroup analysis also showed that patients with HF and a lower functional NYHA class (II) benefit more than patients with more severe symptoms (NYHA class III to IV). Therefore, treatment with dapagliflozin in a patient with HFrEF should be initiated early, preferably before discharge from the hospital or at an outpatient follow-up visit immediately after discharge following hospitalization due to HF exacerbation.

The DAPA-HF study was the first to include patients with impaired renal function (ie, eGFR of 30 to 60 ml/min/1.73 m^2). Despite the initial increase in creatinine levels observed during the study in both dapagliflozin and placebo groups, the effect of the study drug was favorable at further follow-up in patients with both normal and impaired eGFRs.

The DAPA-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) study has recently been completed.[36] It was the first clinical trial to evaluate the benefits and risks of SGLT-2 inhibitor use in patients with various stages of chronic kidney disease, both with T2D and without carbohydrate metabolism disorders. In March 2020, the DAPA-CKD study was terminated prematurely following the recommendation of the independent monitoring committee. The decision to terminate the study prematurely was made after a routine efficacy and safety evaluation that demonstrated the benefit of dapagliflozin earlier than assumed in the study protocol. In July 2020, it was reported that treatment with dapagliflozin was associated with a significant reduction in the primary composite endpoint, which included worsening of renal function (≥50%), development of end-stage renal disease, and death in adult patients with chronic kidney disease regardless of the presence of T2D. In addition, a beneficial effect was achieved in all secondary endpoints, including all-cause death. The safety and tolerability profile of dapagliflozin was consistent with previously published data from other clinical trials.[36,37]

Safety of dapagliflozin Recent large, international, randomized studies on the use of dapagliflozin have revealed the advantages of this drug in reducing the incidence of cardiovascular complications in patients with T2D (the DECLARE-TIMI 58 study),[21] as well as in patients with HFrEF regardless of coexisting T2D

(the DAPA-HF study).[22] Apart from its efficacy, the safety profile of dapagliflozin presented in both publications is crucial.

The studies showed that dapagliflozin is a safe drug. This is indicated by the rarity of adverse events (AEs) leading to treatment discontinuation. The most common AEs included mild-to-moderate fungal infections of the external genitourinary organs, which do not require discontinuation of SGLT-2 inhibitor treatment. The symptoms disappear following treatment with a topical antifungal agent or a single dose of an antifungal drug. In the DAPA-HF study, 14 patients (0.6%) in the dapagliflozin group and 17 (0.7%) in the placebo group had a serious urinary tract infection. According to the results of the available studies, the risk of urinary tract infection is not increased with SGLT-2 inhibitor therapy and should not raise concerns about the implementation of such treatment.

During SGLT-2 inhibitor therapy, osmotic diuresis and natriuresis increase, so patients should be alerted to the need to drink more fluids. If used, the doses of diuretics (particularly loop diuretics) should be appropriately adjusted. The risk of developing orthostatic hypotension is increased in elderly patients taking SLGT-2 inhibitors. Major hypoglycemic events in the DAPA-HF study were observed in 4 patients (0.2%) in the dapagliflozin group and 4 (0.2%) in the placebo group, all of whom had T2D. In both DECLARE-TIMI 58 and DAPA-HF studies, the incidence of AEs related to amputation, fracture, hypovolemia, and renal dysfunction was similar between the dapagliflozin and placebo groups.

Euglycemic diabetic ketoacidosis could be a rare complication of SGLT-2 inhibitor use in patients with T2D. Therefore, patients should be educated about the need to see a physician in case of polyuria, severe nausea and/or vomiting, abdominal pain, severe thirst, and rapid and deep breaths combined with a "sweet," fruity smell of the breath—in these cases, treatment with SGLT-2 inhibitors should be discontinued after immediate medical consultation. These drugs should also be temporarily discontinued during fasting periods (eg, before surgery). Alcohol misuse and ketogenic diets are contraindicated.

According to the Summary of Product Characteristics currently valid in Europe,[38,39] dapagliflozin is indicated:

- in adult patients for the treatment of inadequately controlled T2D, as an additional therapy to diet and exercise, either alone, in the absence of metformin tolerance, or in combination with other medicinal products used to treat T2D
- in the treatment of insufficiently controlled type 1 diabetes as an adjunct to insulin in patients with a body mass index greater than or equal to 27 kg/m^2, when insulin alone does not provide adequate glycemic control despite optimal insulin therapy (dapagliflozin 5 mg)
- in adults, to treat symptomatic HFrEF

In HFrEF, the recommended dose is 10 mg of dapagliflozin once daily in combination with other medications for HF. No dose adjustment is necessary for patients with renal impairment. However, experience with dapagliflozin for the treatment of HFrEF in patients with severe renal impairment (eGFR <30 ml/min/1.73 m^2) is limited, as well as the experience in patients with NYHA class IV. Dapagliflozin is the first flozin approved for use in adults with HFrEF.

Use of dapagliflozin in the treatment of heart failure: patient population The DAPA-HF trial was a groundbreaking study that demonstrated the efficacy of SGLT-2 inhibitors for improving the prognosis of patients with HFrEF. The results of the DAPA-HF study are the basis for the use of dapagliflozin in a wide population—not only in patients with T2D and HFrEF but also in those with HFrEF without T2D.

Currently, over 5 years have passed since the publication of the recent guidelines for the diagnosis and treatment of acute and chronic HF. Since then, the results of new clinical trials on SGLT-2 inhibitors have appeared, expanding our knowledge about their use in various groups of patients, including those with HF. Therefore, experts from the European Heart Failure Association have recently published a position paper on the use of SGLT-2 inhibitors in HFrEF.[40] Based on the available evidence, SGLT-2 inhibitors (empagliflozin, canagliflozin, and dapagliflozin) may be recommended to reduce the risk of hospitalization for HF in patients with T2D and established cardiovascular disease or who are at high cardiovascular risk. Importantly, this position paper did not include the recently published DAPA-HF (dapagliflozin) and EMPEROR-Reduced (empagliflozin) studies. The results of the recent CVOTs with antidiabetic drugs have enriched our therapeutic knowledge and led to changes in both clinical guidelines and drug registrations. SGLT-2 inhibitors are a new class of drugs with a breakthrough significance in the treatment of patients with HF. The collected data will allow them to be placed high in the hierarchy of drugs that alter the natural course of HF.

Practical guidelines for the use of dapagliflozin Recent studies have indicated that SGLT-2 inhibitors will be one of the main groups of drugs used in patients with HFrEF. So far, dapagliflozin (used in addition to ARNIs, ACEIs or ARBs, MRAs, and β-blockers) is the only SLGT-2 inhibitor that has proven effective in reducing mortality in patients with HFrEF. Summarizing the data presented above, let us outline some practical, clinical comments on the use of dapagliflozin in patients with HFrEF.

According to the Summary of Product Characteristics, dapagliflozin should be administered once daily at a dose of 10 mg. It can be taken at any time of the day, with or between meals. In T2D therapy, dapagliflozin can be used alone or in combination with other antidiabetic agents. It is crucial to effectively select patients for the treatment with dapagliflozin.

Dapagliflozin should be considered in:

- patients with HFrEF with left ventricular ejection fraction lower than or equal to 40%[22]
- patients with NYHA functional class II to IV[22]
- patients with or without T2D[22,39]
- patients on standard cardiovascular treatment (ie, β-blocker and / or renin–angiotensin–aldosterone system inhibitor [ACEI / ARB or ARNI], and MRA if recommended)[22]—dapagliflozin can be added to any HF therapy[22]
- creatinine clearance should be greater than or equal to 30 ml/min/1.73 m^2[29,32]

Renal function should be assessed based on creatinine clearance according to the following schedule: before starting treatment with dapagliflozin and at least annually thereafter; before the initiation of drugs that may interfere with kidney function, and then periodically throughout treatment.

The use of dapagliflozin is beneficial while taking medications recommended for the treatment of HFrEF. Dapagliflozin was shown to act synergistically with the drugs recommended by the HFrEF guidelines, regardless of the therapy and target dose used.[22] The clinically significant observation showing that the effect of dapagliflozin was independent of the primary drug therapy supports the hypothesis that SGLT-2 inhibitors act in a mechanistically independent and complementary manner to other HFrEF therapies. Similarly, the dosing of the primary drug and the use of implantable devices (eg, an implantable cardioverter-defibrillator or cardiac resynchronization therapy) do not alter the effect of dapagliflozin, suggesting an additional benefit regardless of optimized HFrEF pharmacotherapy or the use of therapeutic devices.

On October 15, 2020, the European Medicines Agency's Committee for Medicinal Products for Human Use recommended dapagliflozin for approval for the indication of HF and, in November 2020, dapagliflozin was approved in Europe (and therefore in Poland) to treat specifically adult patients with symptomatic chronic HFrEF.[38,39]

SUPPLEMENTARY MATERIAL

The Polish version as well as the extended Polish version of the paper are available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST AS, AW, JD, JG, JK, JN, and PL received lecture and consulting fees from AstraZeneca. AG received lecture honoraria. ML received lecture honoraria from AstraZeneca. EAJ and PP received lecture and consulting honoraria from AstraZeneca and Boehringer Ingelheim. PRo received lecture honoraria from AstraZeneca and Boehringer Ingelheim. Other authors declare no conflict of interest.

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